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Perspective

There Is Still a Need for a Comprehensive Investigation of the Health Consequences of Exposure to Urban Air with Special Regard to Particulate Matter (PM) and Cardiovascular Effects

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Abstract: Air pollution is a foremost public health problem worldwide. The pulmonary effects of air pollution have been well established for decades, and substantial epidemiological evidence is consistently showing that both acute and chronic exposure to air pollution is linked to cardiovascular morbidity and mortality. The underlying cause for this link is, however, still unknown, and many questions remain open. Most of the epidemiological studies focusing on health consequences of exposure to urban air used data from air monitoring stations or—when applying personal sampling or monitoring—measured a limited number of components to assess the exposure. On the other hand, studies conducting a decent exposure characterization and measuring a relatively large number of components with personal sampling had little or no focus on the effects and investigated only a few biomarkers. The number of research studies on this topic is huge, but at the same time, it seems as if there was no need for a comprehensive examination of the effects of urban air pollution on health. Researchers and research supporting organizations, in their fascination with the search for "novelty" and "beyond state-of-the-art", do not seem to be aware of that they will never be able to assemble the whole picture from the puzzle pieces of research activities focusing only on certain aspects. Without a comprehensive investigation, we might never be able to answer such questions as (i) which of the urban air pollutants are forerunners in causing health effects, especially cardiovascular effects? (ii) Which biomarkers have the best predictor performance in early effects? (iii) Are there biomarkers or combinations of biomarkers that can help determine the degree of individual susceptibility and sensitivity and the dependence of these by different factors (e.g., age, gender, and physical activity)? The authors of this article aim to go through the already investigated—at the same time, essential—elements of the topic and propose a more comprehensive study, which, of course, can be expanded, debated, and improved.

Keywords: urban air pollution; exposure assessment; biomarkers; individual susceptibility and sensitivity; project

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1. Why Do We (Still) Need to Deal with Urban Air Pollution? (Importance and Background)

Air pollution is still a major public health challenge today, primarily because of its harmful effects on human health. One encounters issues with air pollution worldwide, even though related problems might be more significant for some countries than for others. An increasing proportion of people live in large cities, where this challenge is exacerbated. Although significant progress has been made in reducing the concentration of air pollutants in cities—e.g., through stricter vehicle emission limits and controls—urban air pollution remains a major daily problem in many countries around the world [1]. The decrease in road traffic and the decline in industrial production due to the COVID-19 pandemic have led to a clear and drastic temporary reduction in air pollution in many places, showing that this problem could be solved very quickly by eliminating sources of pollution or reducing emissions [2,3]. However, these are not feasible without a significant downturn in the economy and a decline in peoples current living standards. If this is the case, more effort needs to be put into revealing and understanding the health aspects of urban air pollution, all with the active involvement of the citizens.

Air pollution is associated with staggering levels of morbidity and mortality. Globally, air pollution is associated with several million premature deaths every single year. The Global Burden of Disease Group has ranked ambient air pollution as the fifth highest risk factor for mortality [4]. It has been estimated that >90% of the worlds population live in levels of pollution above the limits foreseen in the World Health Organization (WHO) Air Quality Guidelines. The European Environment Agency (EEA) reported in 2019 that, in the European Union (EU), the proportion of the urban population exposed to air pollution above EU standards was generally lower than the proportion estimated to be exposed above the WHO guidelines. Still, the premature deaths in EU attributable to air pollutants exposure in 2016 are striking: 374,000 for $PM_{2.5}$, the "fine" fraction of particulate matter (PM), 68,000 for nitrogen dioxide (NO_2), and 14,000 for ozone (O_3) [5]. The pulmonary effects of air pollution have been well established for decades, being known to worsen asthma and respiratory diseases [6,7]. Over the past few decades, there has been a growing indication that air pollution affects many other areas of the human body. Substantial epidemiological evidence is consistently showing that both acute and chronic exposure to air pollution is linked to cardiovascular morbidity and mortality [8,9]. The underlying cause for this link is, however, still unknown, and many questions remain open. For example, how does pollution cause cardiovascular effects, and which air pollutants are responsible for it? These are complex questions; however, studies have shown that the cardiovascular associations are strongest for PM in the air [10]. The European Commission announced a two-stage tender in the Horizon Europe framework program, in 2023, with the following title: "The role of environmental pollution in non-communicable diseases: air, noise and light and hazardous waste pollution". The number of grants and the amount of funding for the supported projects, the supporters expectations for the complex, and the comprehensive implementation of the projects, give hope that research activities will be started in the near future that will bring us closer to answering the open questions [11].

1.1. The Components of Urban Air Pollution

There are many sources of urban air pollution and accordingly many air polluting components. The most common emission sources can be separated into those caused by transportation and residential and personal activities and to those arising from commercially or industrially related sources. Regarding cars, buses, trucks, motorcycles, boats, and other motorized vehicles, various modes of transportation are responsible for most of the air polluting emissions in cities. Traffic density is correlated with the emission of pollutants, their concentration in urban air, and hence human exposure to the potentially harmful chemicals [12]. Pollutants from vehicle emissions are related to vehicle type (e.g., light- or heavy-duty vehicles) and age, operating and maintenance conditions, exhaust

treatment, type and quality of fuel, wear of parts (e.g., tires and brakes), and engine lubricants. The combustion of gasoline and diesel products is a primary emission source of carbon dioxide (CO_2), carbon monoxide (CO), hydrocarbons (HC), nitrogen oxides (NO_x), PM, and substances known as mobile-source air toxics (MSATs), such as aldehydes (e.g., formaldehyde, acetaldehyde and acrolein), benzene, toluene, and 1,3-butadiene. Each of these along with secondary by-products, such as O_3 and secondary aerosols (e.g., nitrates and inorganic and organic acids), can cause adverse effects on human health and the environment [13]. Diesel engines emit more organic compounds and elemental carbon (EC) compared to gasoline engines [14]. Polycyclic aromatic hydrocarbons (PAHs) and nitrated PAHs are also emitted because of incomplete combustion, fuel additives, and other contaminants in the fuel supply [8]. Gasoline engines emit lower amounts of PM compared to diesel engines but larger quantities of semi-volatile and volatile organic compounds (VOCs) [15]. VOCs, such as benzene, toluene, ethylbenzene, and xylenes (BTEX), are released from the fuel itself during the use of engines, from gas-filling stations or portable fuel containers [12]. Traffic-related sources have been recognized as a significant contributor of PM particularly within major cities. Traffic-related PM emissions are composed of—in descending order of concentration—organic carbon (OC), inorganic ions (sulphate, chloride, nitrate, ammonium), metals, and EC [16]. Exhaust and non-exhaust traffic-related sources are estimated to contribute almost equally to traffic-related PM_{10} emissions [17]. Non-exhaust particles can be generated either from non-exhaust sources, such as brakes, tyres, clutches, and road surface wear, or already exist in the form of deposited material at the roadside and become re-suspended due to traffic-induced turbulence. Among non-exhaust sources, brake wear can be a significant PM contributor, particularly within areas with high traffic density and braking frequency. Studies mention that in urban environments, brake wear can contribute up to 55% by mass to the total non-exhaust traffic-related PM_{10} emissions and up to 21% by mass to the total traffic-related PM_{10} emissions, while in freeways, this contribution is lower, owing to lower braking frequency [17]. Despite large variations in the chemical composition of commercial lining materials, most researchers have reported iron (Fe), copper (Cu), zinc (Zn), and lead (Pb) to be the most abundant metals in the brake lining [18,19]. Iron content can reach up to 60 *w*/*w*% and varies according to the type of lining. Copper and Zn follow at relatively high concentrations, while potassium (K) and titanium (Ti) are also present at considerable concentrations. Brake wear emissions have been cited as a potentially important source of antimony (Sb). Brake linings contain 1–5% Sb in the form of stibnite (Sb_2S_3), which is employed as a lubricant to reduce vibrations and improve friction stability [20]. Stibnite can be oxidized during the braking process to antimony trioxide (Sb_2O_3), which has been categorized as a potentially carcinogenic substance [21]. There is a general belief today that traffic-related pollutant emissions would be eliminated by replacing gasoline and diesel engines vehicles with electric cars. It is obvious, however, that such a change would not affect brake wear emissions to a considerable extent.

The abovementioned urban air pollutants can originate from other sources as well. Their contribution to the concentration of pollutants is, however, very variable depending on the extent and type of industrial activities, types of heating and cooling systems, the extent and proximity of waste incineration, and biomass burning, etc. Pollutants can even be generated by natural environments. Parks, gardens, green spaces, roadside trees, and bushes release VOCs to the urban atmosphere [22]. Some of the emission sources—like heating or urban vegetation—show seasonal variations.

1.2. Human Exposure to Urban Air Pollutants

Most people, especially in developed countries, spend more than 90% of their time indoors; hence, they are exposed to urban air pollutants for short periods [23]. Nonetheless, many people are still working in proximity to traffic, being occupationally exposed to emissions from motor vehicles and other urban sources. Several studies investigated

workers◎exposure to different air pollutants, mainly originating from traffic. These papers reveal the association between exposure and health effects to some extent.

Belloc-Santailestra et al. investigated three groups of chemical substances: PAHs, VOCs, and aldehydes (formaldehyde and acrolein) in tollbooths [24]. Concentrations of the total PAH, BTEX, and formaldehyde content varied between 98 and 336 ng/m^3, 5.0 and 40.5 μg/m^3, and 0.06 and 19.1 μg/m^3, respectively. Pilidis et al. reported formaldehyde and benzene exposure levels for policemen in outdoor environments (car, motorcycle, and foot patrol, guards, and traffic regulators) that ranged from about 3 to 25 μg/m^3 and 7 to 36 μg/m^3, respectively [25]. Zhang et al. disclosed breathing-zone concentrations of several carbonyl compounds: formaldehyde (14.1–80.1 μg/m^3); acetaldehyde (8.41–80.3 μg/m^3); acetone (0.65–1096 μg/m^3); acrolein (<0.14–3.71 μg/m^3); propionaldehyde (1.08–14.6 μg/m^3); crotonaldehyde (<0.13–2.80 μg/m^3); benzaldehyde (1.79–9.91 μg/m^3); and hexaldehyde (0.122–22.4 μg/m^3) among garage workers [26]. Davis et al. characterized occupational exposure to eighteen different VOCs and aldehydes (e.g., hexane, benzene, 1,3-butadiene, styrene, acetone, acetaldehyde, formaldehyde) in the U.S. trucking industry, using samples collected at four distinct locations [27]. Sapkota et al. measured the concentration of VOCs and particle-bound PAHs inside and outside the Baltimore Harbor Tunnel tollbooth during the summer of 2001 [28]. The mean outdoor benzene and 1,3-butadiene concentrations varied by shift with the morning (10.7 and 19.8 μg/m^3) exceeding the afternoon (7.2 and 14.9 μg/m^3) and the lowest levels observed during the night (3.7 and 4.9 μg/m^3, respectively) when traffic volume decreased significantly. In comparison, considerable protection was provided to workers by the indoor environment, where lower concentrations of 1,3-butadiene and benzene were observed for all three shifts (2.9 and 6.7, 0.9 and 3.2, and 0.9 and 2.4 μg/m^3, respectively). These studies focused on the exposure of organic substances in air pollution.

There are, however, less data on workers◎exposure to metal compounds and the soluble fraction of metal compounds from traffic-related sources [29,30]. Personal exposure of traffic police officers to PM, CO, and/or benzene was investigated in several studies [31–35]. In the study conducted by Cattaneo et al. mean personal exposure levels of CO, respirable PM, and benzene were 3.51 mg/m^3, 128 μg/m^3, and 11.5 μg/m^3, respectively [35]. The highest ambient mean levels of these components were found during cold seasons. There are occupational groups, such as taxi drivers, whose exposure to traffic-related air pollutants ($PM_{2.5}$, PM_{10}, CO, VOCs, NO_2, SO_2, EC, nitrated PAHs) has been examined in several studies [36]. Other occupational groups, such as street parking attendants and bicycle couriers, might be exposed to the same or even higher concentrations of air pollutants relative to the already mentioned populations; however, their exposure has been much less investigated. The level of air pollutants exposure when working as a bicycle courier is comparable with levels of exposure of other groups of professionals taking part in traffic, but the pulmonary ventilation during cycling can be up to four times higher than the resting value, which causes an increased exposure to traffic-related air pollution [37]. Street parking attendants are most probably exposed to lower concentrations of air pollutants than bicycle couriers. Nevertheless, the variation in exposure levels might be quite large.

1.3. Health Problems Related to Urban Air Pollution

According to the findings from a recent systematic review, there exists an overall high or moderate-to-high level of confidence in an association between long-term exposure to traffic-related air pollutants and adverse health outcomes, such as all-cause, circulatory, and ischemic heart disease, lung cancer mortality, asthma onset in children and adults, and acute lower respiratory infections in children [38].

An animal model has revealed that exposure to PM—as a local effect—exacerbates allergic inflammation in the lung [39]. Ozone exposure caused oxidative stress, inflammatory responses, and immunologic disease in laboratory animals [40]. A study, which

attempted to uncover the molecular mechanism of lung toxicity caused by PM, has shown that lung inflammation induced by $PM_{2.5}$ exposure is mediated by pyroptosis in mice [41].

Exposure to urban air pollutants can cause changes in lung function. Short-term exposure to $PM_{2.5}$, O_3, and NO_2 was associated with lower forced expiratory volume in the first second (FEV1) and forced vital capacity (FVC) in non-smoking adults [42]. Long-term NO_2 and PM_{10} exposure decreased lung function parameters in a longitudinal cohort study [43]. High exposure levels of O_3 can be the cause in the development of asthma [44]. An association between $PM_{2.5}$ exposure and increased asthma incidence in adults was revealed in a large European study [45]. A positive correlation between respiratory symptoms (breathlessness, chronic phlegm, chronic cough, asthma, wheezing, and chest tightness) and the annual mean concentration of PM_{10} was demonstrated in a Swiss study [46]. Urban air pollution is a risk factor in the development of chronic obstructive pulmonary disease (COPD) and lung cancer also in the non-smoking population [47]. Different studies have found that a 10 $\mu g/m^3$ increase in $PM_{2.5}$ concentration can raise the risk of lung cancer incidence by 11–31% [48–50].

Oxidative stress and systemic inflammation in ApoE knockout mice were induced by Beijing ambient PM exposure, which contributed to the progression of atherosclerosis as well [51]. Fine and ultrafine (particle diameter < 100 nm) PM can be redox-active due to their composition and may trigger pro-inflammatory responses. Experimental studies indicate that these properties and responses may influence high-density lipoprotein (HDL) functionality via oxidative pathways. As the protein and lipid components of the HDL is affected, its anti-atherosclerotic characteristics including cholesterol efflux capacity, as well as other anti-oxidative and anti-inflammatory features, might be impaired [52].

Biomarkers of systemic inflammation and injuries, heart oxidative stress and endothelial function were analyzed after exposure to ambient $PM_{2.5}$ and/or O_3 in Wistar rats. The study concluded that $PM_{2.5}$ exposure alone could cause inflammation, injuries in the endothelial and cardiac autonomic nervous system (ANS) functions, and O_3 potentiated these effects induced by $PM_{2.5}$ [53]. An intratracheal instillation of PM_{10} caused prolonged systemic inflammation, the activation of blood leucocytes and damage to the vascular endothelium in rats [54]. Elevated biomarkers of vascular impairments in the aorta with the loss of phospholipid acids in myocardial mitochondria in rats exposed to O_3 or diesel exhaust particles (DEP) alone were observed [55]. The latter animal study—together with others showing, e.g., increased vulnerability to arrhythmia in rat hearts after DEP exposure [56]—substantiates the assumption that DEP might play an important role as a component of urban PM in the development of cardiovascular effects.

Epidemiological studies have shown that there is an association between exposure to PM and increased cardiovascular morbidity and mortality and that these effects are exacerbated by individuals with pre-existing compromised cardiovascular function [57]. Chronic exposure to PM early in life is directly linked to the development of cardiovascular alterations, including heart failure, ischemic heart disease, cerebrovascular disease, hypertension, and heart rhythm disturbances [58,59]. Studies estimated a 10% risk of cardiovascular mortality for each increment of 10 $\mu g/m^3$ in long-term $PM_{2.5}$ exposure [60,61]. $PM_{2.5}$ exposure is associated with an increase in the risk of atrial fibrillation incidence [62] and the high incidence of episodes of ventricular tachycardia and ventricular fibrillation [63]. In addition, the increased likelihood of having developing coronary atherosclerosis [64] and an increased risk of myocardial infarction [65] are also associated with the fine fraction of urban PM. Studies have shown significant associations between higher incidences of hypertension and $PM_{2.5}$ exposure, not only in adults but in adolescents and children as well [59,66,67]. Studies have documented an increased risk of all hypertensive disorders [68,69] and an increased probability of early onset preeclampsia [69] during pregnancy in association with $PM_{2.5}$ exposure.

Apart from the respiratory and cardiovascular health effects, urban PM might play a role in the development of many other health problems. An epidemiological study in the US found a correlation between PM exposure and adult diabetes [70]. A study involving

111 traffic wardens exposed to outdoor pollutants and a control group of 101 administrative employees showed that the diagnosis of an allergy was more frequent in the exposed group than in the controls. Among the exposed workers, those who worked on foot or via motorcycle had a higher positivity in clinical trials compared to the traffic wardens driving cars [71].

Living in areas with high concentrations of PM has been linked to markers of neuroinflammation and neuropathology associated with neurodegenerative conditions such as Alzheimer's disease-like brain pathologies [72–74]. Long-term exposure to $PM_{2.5}$ was associated with an increased incidence of Alzheimer's disease (AD) in a large cohort of patients older than 65 years of age [75]. A significant reduction in white matter on structural brain magnetic resonance imaging (MRI) was observed among elder women (>65 years) exposed to high levels of PM [76]. Exposure to PM might also play a role in exacerbating cognitive dysfunction and enhancing the progression of neurodegenerative processes underlying Parkinson's disease (PD) [75] and AD [76]. Diesel exhaust (DE) exposure may play a special role in these effects as well [72,77].

Recent studies on COVID-19 identified links between death rates and air pollution in several countries [78]. A study conducted in England showed a positive relationship between the concentration of air pollutants, particularly NO_x, and COVID-19 infectivity and mortality [79]. Among patients hospitalized with COVID-19 in New York City, a higher long-term $PM_{2.5}$ exposure level was associated with an increased risk of mortality and intensive care unit admission [80]. There are studies indicating that environmental pollution could even affect the diversity and abundance of resident microbiota in humans [81].

1.4. Possible Mechanisms of the Development of Health Effects Associated with Exposure to Urban Air Pollutants

The inflammatory mechanisms associated with urban air pollution, particularly PM, have been intensively studied over the past 15 years. Review articles provide a proper and detailed overview on the results obtained in these studies [82–85]. It was reported that $PM_{2.5}$ can interfere with the function and phenotype of alveolar macrophages (AM), which take part in clearing and handling deposited particles. When AM are exposed to PM, a Th1-type inflammatory response begins, which leads to the release of cytokines (interleukin (IL)-12, IFN-γ). PM impairs phagocytic capacity mainly via the presence of toxic substances, e.g., PAHs which decrease antigen presentation, and by causing AM to switch to a Th2-dominant profile (IL-4, IL-10, and IL-13) [86,87]. PM has been shown to cause a significant inflammatory response in in vitro and in vivo models, initiated by AM and airway epithelial cells. These cells produce pro-inflammatory mediators after phagocytosing PM that contributes to the lung immune response, leading to oxidative stress and systemic inflammation [88,89]. In vitro and in vivo studies demonstrated that PM—likely due to its composition—can induce high levels of inflammatory markers, such as IL-1α, IL-1β, IL-6, IL-8, IL-17, IL-18, MIP-3α, MIP-1α, MIP-1β, and TNF-α [90–92]. Some components of PM (such as endotoxins or lipopolysaccharides) are potent activators of the NLRP3 multiprotein inflammasome complex, which activates caspase-1, and consequently, mature IL-1β and IL-18 and pro-inflammatory cytokines are released, participating in local and systemic inflammation [93]. In an in vivo study, PM_{10} activated the NLRP3 inflammasome in airway epithelial cells, recruited inflammatory cells to the airways, and upregulated heme-oxygenase-1, increasing reactive oxidative species (ROS) production and causing the release of TNF-α, IL-1, IL-6, and IL-8, IL-17, IL-1β, keratinocyte-derived chemokine (KC), CC chemokine ligand-20 (CCL20), and GM-CSF [91]. $PM_{2.5}$ triggers the NLRP3 inflammasome and induces systemic inflammation, which is associated with increased circulating growth factors and cytokines, such as TNF-α, MCP-1, MIP-1α and MIP-1β, IP-10, IL-1β, and IL-18 [94]. $PM_{2.5}$ can activate AM and airway epithelial cells to release the growth factor, TGF-β1, which stimulates fibroblast proliferation and the epithelial–mesenchymal transition, a process by which epithelial cells transition to a motile mesenchymal phenotype, a marker of epithelial plasticity. This process is associated with an

increase in pro-inflammatory cytokines, such as TNF-α, IL-1β, and IL-6, which prolongs inflammation and can lead to elastin degradation and alveolar destruction [92,93]. Due to its potential immunological effects on the respiratory system, PM exposure can increase susceptibility to viral and bacterial infections by increasing inflammation, which can have harmful effects on AM function [84].

The main pathophysiological mechanism linked to PM exposure in the cardiovascular system are systemic inflammation, impaired coagulation, impaired autonomic responses, and a change in vascular cells, which all together increase the risk of cardiovascular disease (CVD). The mechanisms by which PM exposures promote CVD are not yet completely understood [57]. In the big picture of examining the cardiovascular effects of air pollution, it is important to consider the inflammatory mediators that are released from lung cells after contact with PM because some could spill over to the general circulation or increase liver production of acute-phase proteins (e.g., C-reactive protein (CRP), fibrinogen). An increase in circulating pro-inflammatory mediators (e.g., activated immune cells, cytokines) could thus serve as a pathway to initiate adverse effects on the heart and vasculature.

Various experiments have revealed increased cellular and inflammatory cytokine content, such as IL-6, IL-1β, TNF-α, interferon-γ, and IL-8, of bronchial fluid and sometimes in circulating blood after acute exposure to a variety of pollutants [58]. The pro-inflammatory mediators may contribute to acute exacerbation of CVDs due to the destabilization of atherosclerotic plaques, increasing their likelihood for rupture and thrombosis during the inflammatory response [94]. Circulating leukocytes and the vascular endothelium are activated by inflammatory mediators after PM exposure, promoting cell adhesion and migration, increasing the concentration of vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1), and contributing to atherosclerogenesis [95]. An in vivo study explored the effects of $PM_{2.5}$—by inducing an inflammatory response, vascular endothelial injury and a prothrombotic state—on disseminated intravascular coagulation (DIC) [96]. The NLRP3 inflammasome and its effect on IL-1β and other pro-inflammatory products play a critical role in systemic inflammation regulation [84]. AM produce IL-6 after PM exposure, which induce the synthesis of the acute-phase reactant CRP in hepatocytes [97]. Cytokines like IL-1β and tumor necrosis factor-α (TNF-α) may activate several downstream pro-inflammatory genes in different cell types, leading to an increased expression of adhesion molecules in endothelial cells and the further induction of cytokines and chemokines [98]. Also, tissue factor (TF) expression is induced [99]. TF is the single most important inducer of the extrinsic pathway of the blood coagulation system and may contribute to a pro-coagulant state with increased thrombin generation which is known to be stimulated during inflammation [98]. Furthermore, according to previous studies, a high concentration of ambient ultrafine particles resulted in an increased concentration of circulating CD40L, leading to a higher risk of thromboembolism as well as disturbances in certain inflammatory pathways [100,101]. PM could also stimulate the alveolar epithelium and endothelium to release adhesion molecules activating platelets by P-selectin secretion [102].

Various in vitro and in vivo research projects have shown the effects of pollutant particles and gases to induce oxidative stress [103]. The hypothesis that, besides inflammation, oxidative stress also plays an important role in the mechanism linking air pollution and cardiovascular disease has been confirmed [104]. Positive associations of exposure to $PM_{2.5}$, black carbon, and nitrogen oxides with myeloperoxidase have been described in a group of potentially genetically susceptible participants [105]. Further, raised plasma malondialdehyde (MDA) levels were found in patients suffering from acute coronary events linked to black carbon exposure [106]. In another study, involving garage workers and bus drivers, a higher incidence of oxidative lesions in lymphocyte DNA and blood carbonyl concentrations was observed in correlation with greater exposure to air pollution [107]. In correspondence with the abovementioned effects, associations between several air pollutants and P-selectin have been shown to be accompanied by decreases in

antioxidant levels in red blood cells [108]. According to a study, a strong correlation could be observed between the glutathione system as well as the total antioxidant status and intense period of air pollution during the Beijing Olympics, especially in smokers and elderly people [109]. $PM_{2.5}$ and several chemical constituents may be the major air pollution constituents that contribute to the altered function of some major antioxidant enzymes, including superoxide dismutase (SOD) and glutathione peroxidase (GPx) [110].

In a cross-over trial of controlled human exposure to concentrated ambient particles, it was found that PM exposure induces DNA hypomethylation in humans. It was concluded that the rapid hypomethylation of Alu and TLR4 is an epigenetic mechanism that mediates the effects of particle exposure on blood pressure (BP). TLR4 contributes to inflammation, oxidative stress, and cardiovascular responses, thereby promoting the release of thromboxane A2, a potent vasoconstrictor [111]. PM decreases methylation of the short interspersed nucleotide element Alu and NOS genes and the long interspersed nucleotide element-1 (LINE-1) and increases TLR2 methylation [112]. LINE-1 and Alu sequences are present in several genes related to CVDs, and their hypomethylation has been associated with stroke, hypertension, and ischemic heart disease [113].

2. What Should Be Considered When Investigating the Health Effects of Urban Air Pollution? (Objectives)

The scientific background presented at a considerable length above only provides some insight into the scientific area dealing with urban air pollution and its health consequences. The scientific literature published in this field could slowly fill libraries, but at the same time, we are moving further and further away from seeing and understanding comprehensively the set of problems and challenges of urban air pollution. We are getting closer to understanding the cellular and molecular mechanisms of the development of diseases caused by urban air pollution, but under real exposure conditions, still little evidence has been gathered that these mechanisms would proceed similarly to those that have been found under in vitro and in vivo conditions. While the last two statements are obviously debatable, it is, in any case, likely that a more in-depth and thorough examination of different aspects of the field could lead to new results and would offer insights to better shape the overall picture.

2.1. The Particular Importance of Sampling with Special Regard to PM

In the practice of chemical analysis, the quality of the samples to be analyzed is essential, which is determined by the adequacy of the sampling. The quality of the sample here means how representative it is for the purpose of the analysis. By analogy, the accuracy of the exposure assessment may be decisive for the results obtained in a study of the effects of exposure. Most of the epidemiological studies focusing on the health consequences of urban air exposure used data from urban air monitoring stations or—if applying personal sampling or monitoring—measured only a limited number of components to assess the exposure. Several of the frequently measured components (e.g., PM and its size fractions: $PM_{2.5}$ and PM_{10}) are themselves complex mixtures, which consist of different constituents. On the other hand, studies that involved a decent exposure characterization, applied personal exposure measurements, and determined a relatively large number of components had little or no focus on the effect markers of exposure and investigated only a few biomarkers.

To assess personal exposure to air pollutants, personal exposure measurements are preferred relative to stationary measurements at fixed monitoring stations, the latter being used the most often to assess air quality in urban environments. Fixed monitoring stations can be strongly affected by localized traffic intensity and meteorological parameters. Therefore, data from these stations cannot be utilized automatically as indicators of roadside exposures [114].

PM_{10} and $PM_{2.5}$ are the most often investigated particle fractions in outdoor aerosol measurements. They are often referred to as the PM fractions containing particles with

aerodynamic diameters ≤10 and ≤2.5 μm, respectively. Sometimes, $PM_{2.5}$ and PM_{10} are defined as the "fine" and "coarse" fractions, respectively. These definitions are, however, far from being correct; PM_{10} and $PM_{2.5}$ are defined by the International Organization for Standardization (ISO) as particles which pass through a size-selective inlet with a 50% efficiency cut-off at 10 and 2.5 μm aerodynamic diameters, respectively [115]. It also means that $PM_{2.5}$ is part of PM_{10}; thus, the latter cannot only contain "coarse" particles. According to the definition by ISO, the respirable fraction is the mass fraction of inhaled particles which penetrate to the unciliated airways [115]. The respirable fraction (the respirable fraction, defined by EN 481, is a health-related aerosol fraction. Its origin goes back to 1913, and its existence as well as its relevance is supported by many decades of intensive research in occupational hygiene. PM2.5 became the primary EPA standard only in 1997. Nevertheless, it is confusing that this fraction was referred to, in some quarters, as ◎respirable aerosol◎ reflecting a lack of awareness of the long prior history of particle size-selective sampling. PM2.5 has absolutely nothing to do with respirable aerosol as it is generally recognized among the mainstream of aerosol scientists and—unfortunately—adapted by many other scientific fields [116]) used in occupational health practice is specified by the respirable convention in the European Standard EN 481 and have a median aerodynamic diameter of 4.25 μm [117], which substantially differs from 2.5 μm. Therefore, these two fractions cannot be treated and accepted as being identical. To solve this challenge, both $PM_{2.5}$ and the respirable fraction should be sampled and evaluated in a comprehensive study. In doing so, the two fractions could be compared with each other and with results from other studies, regardless of whether those were performed by scientists working in the field of occupational or environmental health. If occupationally exposed persons are chosen as the subjects of the study, the participants◎full-shift exposure to PM should be assessed by personal measurements.

Particle deposition models show that the respiratory tract deposition is highly dependent on the aerosol particle size [118,119]. Health effects resulting from the deposition of PM in the respiratory tract depend on the dose received, the site of deposition, and the body◎s response to the deposited particles [120]. To estimate the deposited dose of PM, the particle size mass distribution of PM is needed, which can be measured by using cascade impactors (stationary and, if feasible, personal) [121–123]. Personal respiratory deposition samplers offer another means to measure the deposited amount of PM and its size sub-fractions (e.g., ultrafine particles) [124]. Particles can be collected on special grids for being analyzed via scanning electron microscopy (SEM) and/or transmission electron microscopy (TEM) [125]. This combination of techniques (including imaging, X-ray microanalysis and selected area electron diffraction) allows the detailed characterization of individual particles and particle agglomerates.

2.2. Measured Air Polluting Components

2.2.1. Metallic Compounds

Among the components of urban PM, metallic compounds are less investigated in epidemiological studies. Therefore, the collected particle fractions may also be characterized chemically for their elemental composition and solubility/bio-accessibility (the potential bioavailability of metal compounds or species can be investigated by measuring their solubility in artificial human tissue fluids or in samples of natural tissue fluids, such as human serum. In this context, the availability of metal ions from a particular metal compound for absorption can be measured when dissolved in body fluids or their in vitro surrogates. The amount of metal dissolved in this procedure is defined as the bio-accessible fraction [126]) of metal compounds. Epidemiology studies revealed a high correlation between blood Pb and cardiovascular mortality and morbidity [127], while Cu and sulfate have been associated with increased monthly mortality [128]. Burnett et al. found an association of Fe, nickel (Ni) and Zn in $PM_{2.5}$ with short-term mortality, while they reported that the total effect of these components was greater than that of the mass alone [129].

Ostro et al. linked fine particle calcium (Ca), Cu, Fe, Zn, manganese (Mn), Pb, Ti, and vanadium (V) with daily mortality [130], while Hirshon et al. associated previous-day fine particle Zn concentrations with increased pediatric asthma cases [131]. Toxicology studies in healthy volunteers have linked neutrophilic inflammation in lungs with Fe and selenium (Se) [132,133]. Pulmonary injury and inflammation were connected to high concentrations of Fe, Cu, Ni, Pd, and Zn [128], while Schaumann et al. reported a higher inflammatory effect in the lungs of healthy volunteers following metal-rich particle (high levels of Zn, Cu, Ni, and Ca) instillation [134] compared with fractions with a lower metal content [135]. Honda et al. examined the viability and production of IL-6 and IL-8 using the BEAS-2B cell line, derived from human airway epithelial cells, to compare the effects of metals existing with different oxidation states on human airway. Airway epithelial cells were exposed to different metal compounds at different concentrations for 24 h. Both cell viability and the production of IL-6 and IL-8 were affected by the metal compounds in a concentration-dependent manner [136]. Several studies have shown that the soluble fraction of metal compounds might play an important role in the adverse health effects caused by exposure to metal-containing aerosols, including welding fumes [137–139]. Other studies investigated the soluble/bio-accessible fractions of metals in different fractions of airborne PM. A serum simulant [140], simulated lung fluids [141], modified Gamble's solution [142], and water [143] were used to leach the soluble/bio-accessible metal content in the collected aerosol fractions.

2.2.2. Diesel Exhaust (DE)

To assess the participants' exposure to DE, the use of elemental carbon (EC), the core component of diesel particulate matter (DPM), and NO_2 was suggested [144]. Since 2012, when the International Agency for Research on Cancer (IARC) classified diesel engine exhaust as carcinogenic to humans (Group 1) [145], there has been an increasing concern about traffic-related DE exposures. EC is the most often used marker for DE emissions and exposures, given that it is a more selective measure of particulate DE than other components, like CO or NO_2 [146]. Personal full-shift PM samples should be collected to determine EC. As EC—together with other air pollutants—can also originate from heating, air samples must be collected both in heating and non-heating periods to be able to differentiate between traffic and non-traffic-related sources [147]. CO, SO_2, and O_3 concentrations might also be used in the evaluation of the results. The sensitivity of the personal measurement techniques for the determination of these inorganic gases in the urban atmosphere is usually insufficient, and there are limitations on the type of samplers that can be carried by a single person. Therefore, data on these gases—together with the meteorological parameters, such as temperature, humidity, wind speed, and precipitation on all sampling days—might be gained from fixed monitoring stations.

2.2.3. PAHs and VOCs

PAHs are present abundantly on PM_1 aerosol particles, their concentrations being significantly higher in summer than over the other seasons of the year. As the ambient temperature decreases, PAHs will tend to deposit, to a greater extent, on the airborne particles [61,148,149]. Derivatives of PAHs, like nitro-PAHs, may also be formed in the atmosphere and be deposited via dust particles. The quantity of nitro-PAHs is associated with PM_1 and, in a study, correlated with the concentration of nitrogen oxides and with the meteorological variables, temperature and wind speed, as well. In the same study, vehicles with diesel engines were proven influential for the formation of these pollutants [150]. PAHs are carcinogenic, the most harmful one, benzo[a]pyrene being in the class 1 human carcinogen list of IARC. Their emissions showed significant positive linear relationships with mortality from malignant tumors and diseases of the nervous system, as well as the heart and cerebral–vascular system [151,152]. Even PAH concentrations that are considered safe may interfere with the endocrine signaling system via commensal microbiota and alter both environmental and commensal bacterial communities [153].

VOCs are air pollutants originating mainly from traffic and industrial sources and may accumulate on road pavements in dry periods and then be removed by rainwater. These pollutants are toxic and pose high ecological and human health risks. Among them, benzene series pollutants (BTEX) are of specific interest due to their abundance in urban air and their adverse human health and ecological effects [154–156]. When their spatial distribution was studied, it was found that the highest concentrations can be detected along the major roads because of the heavy traffic load [157]. Health effects associated with chronic inhalation exposure to BTEX compounds include neurological disorders, respiratory and eye irritation, hematological disorders, reproductive and/or developmental disorders, cancer (leukemia), kidney and liver illnesses, and gastrointestinal problems (nausea, vomiting) [158]. A wide range of PAHs and VOCs should be measured with different sampling and analytical techniques in the urban atmosphere.

2.3. Selection of the Study Population

In epidemiological research, the selection of the populations to be studied is crucial. A research topic—the health effects of urban air pollution in this context—that affects a large proportion of people on earth requires the selection of representative populations. This is, however, very challenging or almost impossible.

Climatic conditions, including the microclimate, and the structure, conditions, and development level of our country's and region's economy, including the ways in which energy is produced and the types of industrial and agricultural sectors, affect the emission and distribution of air pollutants. Therefore, differences in air pollution levels can be huge between countries and even between regions within the same country; hence, they may cause dissimilar health outcomes. The lifestyles and habits of society, in general, and of the people in our proximity have a significant impact too. While emissions of pollutants from transport in Western developed countries are steadily declining, owing to environmental regulations, cleaner diesel and gasoline engines, and the growing use of electric vehicles; wood burning is becoming more widespread also in large European cities [159]. The residential burning (often open burning) of waste and biomass can add to this problem, especially in districts with a population that has lower incomes [160].

2.3.1. Age Aspects

One crucial factor is age. Studies have shown that the severity or even the existence of the effects can be age-dependent. A study investigated the association between the exposure to particle-rich air collected above a busy street and microvascular function (MVF) assessed non-invasively by measuring digital peripheral artery tones following arm ischemia. Hemoglobin, red blood cells, platelet count, coagulation factors, CRP, fibrinogen, IL-6, TNF-α, lag time to the copper-induced oxidation of plasma lipids, and protein oxidation measured as 2-aminoadipic semialdehyde in plasma were markers of the possible health effects, such as atherosclerosis. The results of the study indicated that exposure to air pollution particles at outdoor concentrations is not associated with detectable systemic inflammation, lipid, protein oxidation, altered hemostasis, or MVF in young healthy participants [161]. A very similar study conducted by the same researchers concluded that the reduction in particle exposure via the filtration of recirculated indoor air for only 48 h improved MVF in healthy elderly citizens, suggesting that this may be a feasible way to reduce the risk of CVD [162].

The short-term effects of particle size fractions on circulating biomarkers of inflammation were investigated, in a study, in a panel of elderly subjects and healthy young adults. The obtained results revealed different associations between the different size fractions (PM_{10}, $PM_{2.5–10}$, $PM_{2.5}$, $PM_{1–2.5}$, PM_{1}) and the biomarkers (white blood cells, IL-6, high-sensitivity CRP, TNF-RII) measured in blood sera of the elderly and young adults [163]. Cardiovascular and lung function in relation to outdoor and indoor exposure to fine and ultrafine PM in middle-aged (41–68 years old) subjects were examined in a study. MVF was significantly inversely associated with particle number concentration (PNC) in the

outdoor environment, while exposure to PNC and bio-aerosols appeared to have adverse effects on lung function and some markers of systemic inflammation and diabetes. The associations were not dependent on age or gender [164]. A study examined the associations between PM exposure and endothelial function among workers (19–64 years old) in Norwegian smelters. PM exposure was associated with a higher baseline pulse amplitude (BPA) (the baseline pulse amplitude (BPA) reflects microvessel pulsatility and has been shown to correlate with important CVD risk factors, such as advancing age and higher blood triglyceride concentrations [165,166]) among participants older than 34 years. This result may indicate an age-dependent cardiovascular susceptibility to PM exposure [167].

2.3.2. Gender Aspects

The gender aspects of air pollution have been less intensively investigated than others, despite the suggestion based on some studies that a greater main effect of air pollution on respiratory outcomes can be expected for women as compared to men [168]. One among the few studies focusing on women found that prior year exposures to $PM_{2.5}$ and O_3 are associated with adverse effects on inflammatory and hemostatic pathways for cardiovascular outcomes in midlife women [169].

2.3.3. Physical Activity

A few studies proved that urban air pollution worsens pre-existing respiratory and cardiovascular diseases [170]. At the same time, there are factors, such as physical activity, that have a considerable capacity to decrease the prevalence of cardiovascular risk factors, including arterial hypertension. Consequently, physical activity can counteract the harmful effects of air pollution. Also, exercise can induce anti-inflammatory effects, mainly by controlling the production, release, and activity of TNF-α and IL-6 [171]. Another study, however, concluded that in highly polluted areas, frequent exercise might protect against $PM_{2.5}$-associated arterial stiffness but exacerbate airway inflammation [172].

2.3.4. Lifestyle and Stress

Lifestyle risk factors, including dietary habits, physical inactivity, smoking, and adiposity, strongly influence cardiovascular risk factors, such as dyslipidemia, hypertension, or diabetes mellitus, and affect novel pathways of risk, e.g., inflammation/oxidative stress, endothelial function, thrombosis/coagulation, and arrhythmia [173]. Psychosocial stress and stress conditions are independently associated with CVD in a manner that depends on the degree and duration of stress as well as the individual response to a stressor [174].

While lifestyle risk factors are often considered in the evaluation of the effects possibly caused by exposure to urban air pollution, psychosocial stress is very rarely considered. A quite recent study investigating the association between psychosocial stressors (depression, acculturation, perceived stress, discrimination, negative life events) and ambient particle number concentration found that for Puerto Rican adults, cardiovascular non-innate susceptibility to adverse effects of ambient particles may be greater for women under high stress [175]. Mental health factors (e.g., anxiety and depressive symptoms) and the role of these factors in the responses to environmental effects (in this case, exposure to urban air pollutants) could be investigated.

2.3.5. Effect of the Duration of Exposure

Worker groups (e.g., bicycle couriers and street parking attendants) that are occupationally exposed to urban air pollutants are suggested as the study populations. These groups of people might not be able to appropriately represent the entire population affected by urban air pollution, but there might be some reasons and even advantages that can underline this choice. It has been mentioned before that there seems to be no safe level of air pollutants, which means that even low exposures to air pollution can cause health effects. If one is interested in the exposure–effect relationship, however, there is a higher

probability to find and detect an effect at higher exposure levels. This is a classical toxicological approach, which—to retrieve an effect—in some in vitro and in vivo experiments led to such an overdose (of, e.g., TiO_2 nanoparticles) that was far from a realistic exposure situation [176]. On the other hand, not all the epidemiological studies under realistic conditions have found significant associations between exposure and the effects. In a Dutch study, air pollution exposure during commuting (by bus, car, or bicycle in the morning rush hour) was not consistently associated with acute changes in inflammation markers, blood cell counts, or blood coagulation markers in healthy adults. It is likely that these results were due to the low doses received by the study participants; however, other factors (like timing of the health measurements) cannot be excluded [177]. Street parking attendants are more exposed to urban air pollutants than other residents, due to the proximity of traffic. The exposure might be even higher for bicycle couriers, who actively take part in traffic. Both groups are occupationally exposed to potentially harmful chemicals, so there is a responsibility to deal with their health condition also from an occupational health point of view. Due to the changing habits of urban citizens, namely that more and more people order food from home, there has recently been a large increase in the number of food couriers, including bicycle couriers. Compared to the still growing size of this occupational group, most of the studies dealing with on-road bicyclists◎exposures focused on travelers (e.g., commuters) and not on bicycle couriers [178]. Since one of the explicit aims is to examine how health effects develop, healthy participants (those who were not diagnosed with a chronic illness) should form the study population. In the case of a sufficiently large number of volunteers, parameters such as age or gender can also be successfully examined from a statistical standpoint. In addition, factors that are more difficult to assess, such as physical activity, can be accurately measured by bicycle couriers, at least during work. In case of lifestyle risk factors, psychosocial stress conditions as well as mental health conditions, the study groups should appropriately represent a larger urban population.

2.4. Biomarkers of the Health Effects

The biomarkers to be analyzed may be chosen based on the currently available scientific literature and might be complemented at the start of an actual project. A few of the pulmonary and systemic inflammatory markers are highlighted here, which are currently the most common in the examination of the acute effects of exposure to urban air pollution: (i) Clara cell protein 16: CC16 is excreted from non-ciliated Clara cells of the bronchial epithelium and traverse the biological membranes of the lungs into the serum compartment of the blood [179]. CC16 is considered a biomarker of epithelial lung injury. (ii) Surfactant protein D: Surfactant proteins (SP) A and D are synthesized mainly in the pulmonary Clara cells, pneumocytes type II, goblet cells and in glandular tracheo-bronchial cells. The functions of SP-A and SP-D are mainly related to immune defense and to the regulation of inflammation [180]. It has been proposed that SP-D may be a better serum biomarker of lung injury than SP-A. The concentration of both biomarkers in serum is increased in several lung diseases that are characterized by mucosal inflammation or parenchymal injuries. (iii) KL-6/MUC-1 (KL-6) is a useful biomarker in the diagnosis of various types of interstitial lung diseases. KL-6 is a circulating high-molecular glycoprotein, classified as human MUC-1. KL-6 is expressed on the surface membrane of alveolar epithelial cells and bronchiolar epithelial cells [181]. Both KL-6 and SP-D are reportedly elevated in idiopathic pulmonary fibrosis patients and related to the severity of pulmonary fibrosis [182]. (iv) Micro-CRP: CRP (C-reactive protein) is a protein (pentraxin) that increases substantially in concentration during severe inflammation and is an important activator of the complement reaction system [183]. Animal models have indicated a role for CRP in atherogenesis, possibly related to blood coagulation. The half-life of CRP is around 19 h [184]. (v) D-dimer is a measure of fibrin degradation and thus an indirect measure for the formation of thrombi. The level of D-dimer is typically increased during several disturbances in the coagulation system (e.g., venous thrombosis, DIC syndrome) [185].

Reactive oxygen species (ROS)—which are generated due to oxidative stress induced by particles and gases—have short half-lives and consequently cannot be accurately measured directly; instead, substances damaged as a result of ROS can be investigated. ROS can cause the formation of protein and lipid peroxidation products [186], which can be used as biomarkers for oxidative stress [187]. Hydrogen peroxide is one of the major reactive oxygen species. Malondialdehyde refers to the state of lipid peroxidation, protein carbonyl is an indicator of oxidative protein damage, while 8-hydroxy-deoxy-guanosine is a DNA damage marker. Glutathione (reduced and oxidized), glutathione peroxidase, catalase, and superoxide dismutase are prominent members of the antioxidant system [82].

Both the inflammatory and the oxidative stress-related gene activities should be monitored to establish the connections between the different pathways leading to inflammatory responses after exposure to urban air pollutants. Gene activity surveys or multiplex quantitative polymerase chain reaction (qPCR) systems can be used to detect multiple gene expression changes simultaneously. In accordance with the measurement of the abovementioned biological markers, inflammation-related and oxidative stress-related genes should be monitored. The applied qPCR systems should be capable of measuring the gene expression levels of 84 individual genes simultaneously, hence giving an extremely high amount of information from one measurement. After evaluating the results of these measurements, the genes with the most prominent expression rate changes should be selected, and then one can focus on these genes with individually designed primers. The examination of genetic markers in addition to biomarkers may provide additional information on the cascade processes induced by the inhaled air pollutants, since gene activation is not always manifested in protein production.

In summary, a study comprehensively investigating the health consequences of exposure to urban air should answer the following questions:

i. Which of the urban air pollutants play the biggest role in the development of health effects, particularly cardiovascular effects?
ii. The combined effects that can occur upon exposure to several harmful substances at the same time should be investigated. The impact of different concentration levels of air pollutants on the measured biomarkers, and thus on the size of the effect, should also be assessed.
iii. Which biomarkers have the best predictor performance, especially in early effects?
iv. Are there biomarkers or combinations of biomarkers that can help determine the degree of individual susceptibility and sensitivity and the dependence of these by different factors (e.g., age, gender, and physical activity)?

The idealistic purpose of upcoming research is to give an estimate of the individual susceptibility and sensitivity and thus the personal risks of urban air pollution. By openly sharing research results, data, and samples, other research groups should have the opportunity to attain new results and draw new conclusions by conducting studies from other perspectives. One area where further research could be carried out with the use of the collected biological samples is epigenetic research that has already revealed associations between exposure to air pollutants and changes to the epigenome [188] or reduction in epigenetic marks [189] (see also the last paragraph of Section 1.4.).

3. Methodology to Comprehensively Investigate the Health Consequences of Exposure to Urban Air Pollution (Implementation)

The related research objectives could be realized through the implementation of carefully planned and effectively performed activities which are presented in Table 1. It is intended to measure many air pollutants and biomarkers simultaneously in one comprehensive study. An exposure assessment should be completed via a detailed urban aerosol characterization. Statistical analyses need to be carried out thoroughly by using the most state-of-the-art statistical methods.

Table 1. Activities of the proposed project to comprehensively investigate the health consequences of exposure to urban air.

PROJECT CORE ACTIVITIES
1. Selection of healthy volunteers based on medical examinations
2. Air sampling: active (with sampling pump) personal sampling (also on the day off)
2.1. PM fractions (+ inorganic substances): via respirable, $PM_{2.5}$, personal impactor samplers [122,123]
2.2. Markers of diesel exhaust exposure: 25 mm "total" cassettes equipped with quartz fiber filters and sodium iodine-impregnated filter pads [144]
2.3. Organic substances: black 37 mm cassette filter holder 2 μm pore size, PTFE membrane filter connected to a custom-made sorbent tube with different adsorbents (e.g., XAD-2) [190]
3. Blood sampling: from the cubital vein in vacutainer tubes and separated via centrifugation
4. Analysis of the air samples
4.1. PM fractions: gravimetric determination via a six-place microbalance
4.2. Markers of diesel exhaust exposure: elemental carbon (EC) via OCEC Dual Optical Analyzer [191], NO_2 as nitrite via spectrophotometry [192]
4.3. Soluble/bio-accessible metal compounds: after leaching with a lung fluid simulant (e.g., Gamble® solution) via inductively coupled plasma mass spectrometry (ICP-MS) [193]
4.4. Insoluble metal compounds: after digestion with mineral acids via ICP-MS [193]
4.5. Organic compounds (PAHs, nitro-PAHs, VOCs): via high-performance liquid chromatography (HPLC) coupled with fluorescence detection (FL-HPLC) and via gas chromatography–mass spectrometry (GC-MS) with electron ionization (EI) [149,151]
5. Blood/serum/plasma analysis
5.1. Inflammatory markers: e.g., sCD40L, EGF, eotaxin/CCL11, FGF-2, Flt-3 ligand, G-CSF, GM-CSF, GRO, IFN-α2, IFN-γ, IL-1α, IL-1β, IL-1ra, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12 (p40), IL-12 (p70), IL-13, IL-15, IL-17A, IP-10, MCP-1, MCP-3, MDC (CCL22), MIP-1α, MIP-1β, TGF-α, TNF-α, TNF-β, VEGF, CRP via Luminex xMAP technology
5.2. Coagulation and cell adhesion markers: e.g., fibrinogen, D-dimer, PAI-1, soluble CD40L, P-selectin, ICAM-1, VCAM-1 via Luminex xMAP technology
5.3. Markers of oxidative stress: e.g., hydrogen peroxide, malondialdehyde, protein carbonyl, 8-hydroxy-deoxy-guanosine, glutathione (reduced and oxidized), glutathione peroxidase, catalase and superoxide dismutase via specific ELISA and colorimetric assays
5.4. Gene expression rates: inflammatory cytokines and receptors, oxidative stress pathway via RT2 Profiler PCR Array Kits with a real-time PCR system
6. Statistical analysis • Special emphasis on thorough reporting of descriptive variables • Generalized linear mixed-effect models to control for known biases and confounders • Using state-of-the art machine learning (ML) algorithms [194,195]
6.1. Evaluation and discussion of the results
6.2. Dissemination and communication of the results/findings
ACTIVITIES IN CO-OPERATION WITH THE PROJECT

7.	Urban aerosol characterization: stationary/personal size-fractionated PM samples collected via cascade impactors, measurements with particle sizers and counters and via electron microscopic techniques [121,196,197]
8.	Metabolomic profiling of blood via LC-MS/MS system (agreement with the respective researchers)
	SYNERGIC ACTIVITIES WITH THE PROJECT (through openly sharing results and biological samples)
9.	Investigation of the role of mental health factors (e.g., anxiety and depressive symptoms) in the responses to environmental effects (urban air pollution)
10.	Epigenetic research
11.	Exploration of new effect biomarkers of exposure to urban air pollutants and developing new or more effective method for the determination of new or existing biomarkers.

3.1. Study Design and Subjects

Budapest, the 14th most populated city in Europe (2018), has a relatively old car fleet, and the residential burning of wood, waste, and biomass is also a problem in some of its districts, especially in winter. Thus, Budapest offers an excellent location to investigate the problems still present today which affect the urban air quality and human health. Factors at the individual level can be very significant in deciding on how one responds to exposure to air pollutants. In the proposed project, two different populations should be studied: bicycle couriers and street parking attendants. All participants should be healthy volunteers who have not been diagnosed with, e.g., any chronic vascular or heart diseases, cancer, rheumatoid diseases, diabetes, chronic inflammatory disease, or acute inflammation (e.g., sinusitis, pneumonia). Smokers and persons with known alcoholism or drug abuse should not be considered for inclusion. The study participants should be duly informed of the study's nature, significance, implications and risks, and they should be asked to read and sign an informed consent. The information given to the participants (also in form of information sheets) should contain the procedures implemented in the event of unexpected or incidental findings. Participants should have the right "not to know" if they choose this option, or they will be informed of any result that adversely affects their health.

The recruitment is obviously the most critical part of this research that carries the greatest risk of failing to achieve the research objectives. All the other potential risks of the proposed project, such as changes in the research team, equipment failure, and budget problems (e.g., due to rising prices), are minor compared to this risk. The other risks can be minimized by careful planning already in the preparation phase and throughout the project, the use of good project management practices, and regular project evaluations at the operative level. Even if the bicycle courier companies and the largest bicycle NGOs as well as municipalities responsible for street parking are contacted, and these stakeholders all express their interests, the success of the sampling campaigns still depends on the persuasion of the individuals to participate. Therefore, in addition to the information normally given to participants of such epidemiological studies, all potential participants should be acquainted with the purpose and significance of the research, the most important details of the implementation, the expected results, and their utilization. With the use of the principles of open and responsible research as well as citizen science, the organizer of such a project should do their utmost to involve the participants as much as possible. To this end, one should ask for the participants' opinion on planning the practical implementation of sample collection (co-design), and one should develop an incentive system (giving everyone the same rewards) to achieve the most active and enthusiastic participation. Participants should be involved in the discussion of the results to the extent that their interest allows (co-assessment).

Ideally, each group should consist of 150 people, 75 women and 75 men. By involving an equal number of women and men, gender specific mechanisms and pathways should also be possible to investigate. The research should focus on the 25–50 age group, where

the chances of an early onset of health effects, including cardiovascular effects, are the highest. Personal air samples should be taken on a working day and a day off on each study participant during a sampling campaign. Since there is exposure—although much lower—to air pollutants on days off too, assessing this is also an important part of controlling the parameters, rather than assuming that exposure on the day off is negligible compared to the working day. Blood samples should be collected two times from everyone; after the full-day shift at work and on the day off, thereby making each participant—comparably to the case-crossover study design (the case-crossover design is an approach which has been frequently used for studying acute effects of day-to-day variation in air pollution on morbidity and mortality [198]. In this study design, there is a case and a control component, both of which come from the same individual. Each case is self-matched by serving as its own control. Determining the control and case components period is, however, a critical aspect of a case-crossover study [199])—their own control [199]. The order of the sampling days (working day or day off first) may be randomized. Six sampling campaigns should be conducted in a 3-year period by collecting samples both in winter (from the end of November until the beginning of March) and summer (from the end of May until the beginning of September) seasons. Fifty individuals (25 females and 25 males) should be included in each campaign from each study group. The two seasonal campaigns within the same project year should include the same people from each study group. Where possible, the same individuals should be involved in multiple project years, allowing for longer-term changes to be tracked, so that prospective or longitudinal aspects might be included in the evaluation of the results. With 300 participants, with a total of 4 personal air samples and 4 blood samples per person, as well as with the extremely large number of measured parameters both in urban air and blood, this research would be among the most ambitious ones within this research field. Although achieving an even larger sample size should be desirable in terms of statistical power, such a study with a larger sample size is no longer feasible due to human and material resource constraints (the estimated budget of the proposed project reached EUR 3 million already in 2020 (calculated with Hungarian salaries and minimal investment in equipment). The research was planned to be conducted by a group of seven researchers who are experts of their respective scientific fields (exposure assessment, aerosol research, biological monitoring, environmental analysis, atomic spectrometry, chromatography, fluorimetry, colorimetry, quantitative protein analysis, toxicology, molecular genetics, cardiology). Post-doctoral associates (2) and PhD students (2) should also be involved, as well as technicians (2–3) who should do the preparation before samplings, sample collection, sample preparation for chemical analysis and less complex analytical tasks. The estimated full-time equivalent (FTE) was between 7 and 8 for a 5-year project).

3.2. Medical Examinations

For the selection of the healthy ones and to get good baseline health data, all voluntary participants should undergo a structured interview, including the registration of medical history and information on smoking and alcohol habits. The physical examinations should include heart and lung sounds, the registration of weight and height for the calculation of body mass index (BMI), the measurement of blood pressure (BP) and peak expiratory flow (PEF), electrocardiography (ECG), and blood testing for cholesterol and triglyceride levels. In case of deviation from normal values, these examinations should be completed with echocardiography and carotid ultrasonography. On the exposure and control days, PEF might be recorded. During the personal sample collections, the participants◎heart rate (possibly blood oxygen level and BP) should be recorded with appropriate ("pulse") watches.

3.3. Collection and Analysis of Air Samples

Personal full-shift PM samples should be collected in the participants◎breathing zone with respirable cyclones, personal $PM_{2.5}$ samplers, and 25 mm "total" sampling cassettes

to assess their exposure to respirable dust, $PM_{2.5}$, and EC (as a marker for DE), respectively. A respirable cyclone produced by JS Holdings (or similar) and Model 200 Personal Environmental Monitor equipped with 5.0 μm pore-size PVC membrane filters are suggested to be used for the collection of respirable dust and $PM_{2.5}$, respectively. The respirable cyclones and the $PM_{2.5}$ cassettes should be operated at a flow rate of 2.2 and 2.0 L/min, respectively. The 25 mm "total" cassettes should be equipped with 25 mm quartz fiber filters and should be operated at a flow rate of 2.0 L/min. A sodium iodine-impregnated cellulose filter support pad can be placed after the quartz fiber filter by inserting an extra ring into the standard three-part 25 mm aerosol filter cassette to simultaneously collect NO_2 in parallel with EC [144]. For the measurement of PAHs and VOCs in the urban air, a modified standard sampling method should be applied [190], originally developed for the sampling of PAHs. In this method, a 37 mm, 2 μm pore-size PTFE membrane filter and a cellulose spacer ring is put into a black 37 mm cassette filter holder which is connected with minimum length of PVC tubing to a sorbent tube containing washed XAD-2 resin. The sorbent tube is connected to a personal sampling pump maintaining a flow rate of 2.0 L/min. In the proposed project, custom-made sorbent tubes should be applied containing other appropriate sorbent materials (e.g., Chromosorb) than XAD-2 to sample as many organic substances with one sampler as possible. The appropriate flow rates should be maintained by personal sampling pumps (models can vary).

The collected aerosol particulate masses should be determined gravimetrically via a six-place micro-balance in a weighing room dedicated to low filter mass measurements, under controlled relative humidity (40 ± 2%) and temperature (20 ± 1 °C) conditions. EC should be determined by using an OCEC Dual Optical Analyzer according to NIOSH Method 5040 [191]. The soluble/bio-accessible metal fraction of the collected respirable dust and $PM_{2.5}$ fraction should be analyzed after a leaching procedure in which a selected lung fluid simulant (e.g., Gamble's solution or Hatch's solution) should be applied. The non-soluble fraction of the filter samples should be digested with strong mineral acid mixtures in autoclaves. Element contents of the bio-accessible and non-soluble fractions should be determined by inductively coupled mass spectrometry (ICP-MS) [193]. Particulate oxidative potential (OP) should be assessed via antioxidant depletion using a synthetic respiratory tract lining fluid (RTLF) model which is sensitive to intrinsic redox-active PM constituents such as redox-active metals and quinones [200]. The NO_2 is reduced by iodide on the impregnated filter pad to nitrite (NO_2^-), which should be extracted with water. The amount of nitrite should be determined via spectrophotometry via diazotization to a red complex at 540 nm [192]. PAHs concentrations in the air samples should be determined via high-performance liquid chromatography (HPLC) coupled with fluorescence detection (FL-HPLC) or gas chromatography–mass spectrometry (GC-MS) with electron ionization (EI) [148,149,151]. The concentrations of BTEX, as well as other VOCs, like aldehydes in the air samples, should be determined via GC-MS with EI [155,201]

3.4. Collection, Storage, and Analysis of Blood Samples

Blood should be collected from the cubital vein in 8 mL vacutainer tubes and separated via centrifugation at 1900× *g* for 15 min. Sample aliquots should be pipetted into 1.0 mL NUNC® polypropylene cryotubes and stored in a freezer (−18 °C) until analysis. A few mL of the samples should be stored at −80 °C for five years for further analysis until 5 years after the end of the project. It is important to collect the blood samples at the same time of the day in the case of each participant both on the working day and on the day off.

The high-throughput Luminex xMAP technology should be used to estimate the concentration of a wide range of inflammatory mediators in blood plasma, performing the Milliplex® Human Cytokine/Chemokine Multiplex Assay Kit (Cat. Nr.: HCYTMAG-60K-PX38, Merck, Millipore, Darmstadt, Germany). The following key immunological analytes could be quantified: sCD40L, EGF, eotaxin/CCL11, FGF-2, Flt-3 ligand, fractalkine, G-CSF, GM-CSF, GRO, IFN-α2, IFN-γ, IL-1α, IL-1β, IL-1ra, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12 (p40), IL-12 (p70), IL-13, IL-15, IL-17A, IP-10, MCP-1, MCP-3, MDC

(CCL22), MIP-1α, MIP-1β, TGF-α, TNF-α, TNF-β, VEGF, CRP, and soluble TNF receptor. Further, the concentration of coagulation and cell aggregation markers should be also determined via the Luminex xMAP-based method; namely fibrinogen, D-dimer, PAI-1, soluble CD40L, P-selectin, ICAM-1, and VCAM-1 should be quantified.

The Luminex assay should be carried out according to the manufacturer's instructions. Briefly, blood plasma samples should be thawed and tested in a blind fashion and in duplicate. Moreover, 25 µL of each sample or standard should be added to a 96-well plate, followed by the addition of 25 µL capture antibody-coated bead sets to each well. After overnight incubation, the biotinylated detection antibody mixture and the streptavidin–phycoerythrin conjugate should be added to the plate following appropriate washing steps. After the last washing step, 150 mL drive fluid should be added to the wells, and the beads should be resuspended for 5 min on a plate shaker and read on the Luminex Intelliflex® instrument. Luminex xPonent 4.2 software should be used for data acquisition. Five-PL regression curves should be generated to plot the standard curves for all analytes via the Milliplex Analyst 5.1 (Merck Millipore, Darmstadt, Germany) software, calculating with bead median fluorescence intensity values.

To get a comprehensive overview of the redox homeostasis, the following parameters of the oxidative state should be analyzed from blood plasma samples via specific ELISA and colorimetric assays: hydrogen peroxide, malondialdehyde, protein carbonyl, 8-hydroxy-deoxy-guanosine, glutathione (reduced and oxidized), glutathione peroxidase, catalase, and superoxide dismutase.

The gene expression rate examinations should be carried out via RT2 Profiler PCR Array Kits (Quiagen, Hilden, Germany). The kits "Human Inflammatory Cytokines & Receptors" (PAHS-011Z) and "Human Oxidative Stress Pathway Plus" (PAHS-065Y) should be used. The PCR reactions should be performed according to the instructions of the manufacturer. The buffy coat of the blood samples should be used. The messenger RNA should be extracted from the samples using the recommended Qiagen RNA Mini Kit, and the complementary DNA from the extracted mRNA should be synthetized via the recommended Qiagen RT2 HT First Strand Kit according to the instructions of the manufacturer.

To gain even more information from the blood samples from the study participants, metabolomic profiling should be carried out with an MxP® Quant 500 Kit applied in a system consisting of an ultra-high performance liquid chromatograph coupled with the SCIEX Triple Quad5500 LC-MS/MS system. Furthermore, 630 metabolites from 26 biochemical classes (e.g., amino acids, fatty acids, acylcarnitines, phosphatidylcholines, cholesteryl esters, triglycerides) could be determined in plasma from the study participants. The requested sample amount is only 10–20 µL.

3.5. Urban Aerosol Characterization

During the sampling campaigns, stationary size-fractionated PM samples should be collected with a 13-stage Model 125R nanoMOUDI cascade impactor (Microorifice Uniform Deposit Impactor; MSP Corporation, TSI, Shoreview, MN, USA) or a similar impactor type to gravimetrically determine the particle size mass distribution in the range of 0–10 µm aerodynamic diameter. The distribution of the elements as well as the distribution of the bio-accessible and non-soluble metal components might be determined between the different size fractions. For the determination of the particle number size distribution of the aerosols in urban air, stationary particle sizers and counters should be applied (in a project led by the first author of this paper—together with a nanoMOUDI cascade impactor—a scanning mobility particle sizer (SPMS) instrument (model 3938, TSI Inc., Shoreview, MN, USA), equipped with an electrostatic classifier (Model 3082) with a differential mobility analyzer (Long DMA Model 3081A) and an ultrafine condensation particle counter (CPC, Model 3756) was used for the measurement of particles with a mobility diameter between 17 and 542 nm. An aerodynamic particle sizer (APS, Model 3321, TSI Inc., Shoreview, MN, USA) was also used, which detects particles within the size range of 0.542–19.8 µm aerodynamic diameter). Particles should be collected on copper TEM

grids with holey carbon film with a hand-held ESPnano model 100 electrostatic deposition sampler (ESPnano Inc., Spokane, WA, USA) [202]. Elemental composition, morphology, and size distribution of the primary particles that appear as single particles or are distributed in agglomerates should be studied via SEM and/or TEM [197,203].

3.6. Statistical Analyses and Data Management

Studies in this field have typically low to moderate sample sizes. Therefore, our outlined study design is unique in that it will allow us to use intricate statistical methods. To understand and quantify the effects of air pollutants on health effects, we plan to use generalized linear mixed-effect models to control for known biases and confounders. Although these models are fundamental for furthering our understanding of the relationship between air pollutants and their effects, they are often outperformed in predictive power by other approaches, such as machine learning (ML) algorithms [204]. Therefore, to assess the predictive performance of biomarkers on potential health outcomes, we will use state-of-the art ML algorithms (e.g., random forests, neural networks, support vector machines, generalized boosted models) in an ensemble fashion (i.e., multiple model predictions are incorporated into a single prediction outcome) [194,195]. In a field where sampling is costly and is carried out on various populations of vastly different pollutant exposures, transparently reporting descriptive variables is a necessity. Our reports will place special emphasis on the thorough reporting of descriptive variables to facilitate easier comprehension, set an example for future studies in the field, and allow obtained results to be incorporated into future meta-analyses [65,205].

Data management should be carried out in accordance with the guidelines set out in the Horizon Europe Program, including the FAIR principles and other open science practices. Open access to all data should be provided through a trusted data repository (certainly except for personal data) generated in the research so that these data can be used by other research groups.

3.7. Project Timeline

The project can be divided into 6 main activities, including the following: management of the project, selection of the study participants, field work with sample collection, analysis of the collected samples (including analytical method development and/or adaptation), data evaluation, dissemination, and communication (Table 2). These activities are partly built on each other, but they can also run in parallel. The overall progress of the project should be evaluated at the end of each project year, and a final evaluation should be made at the end of the project.

Table 2. The timeline of the proposed project to comprehensively investigate the health consequences of exposure to urban air. The quarter in which the activity is performed is indicated with X.

Activity	Year 1				Year 2				Year 3				Year 4				Year 5			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Management	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Selection of study participants	X	X			X	X				X	X									
Field work, sample collection			X		X		X		X		X		X							
Analysis of the samples			X	X	X	X	X	X	X	X	X	X	X	X	X					
Data evaluation					X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Dissemination, communication							X	X	X	X	X	X	X	X	X	X	X	X	X	X

4. Conclusions

Examining any complex effect and the consequences of this effect requires great thoroughness and the most comprehensive approach possible. The effects of urban air

pollution and some of its components on human health have been studied by many researchers and in great detail. Many results have been achieved, both in terms of exposure assessment and the description of health effects and the mechanisms leading to their development. There is often no lack of a comprehensive viewpoint, but at the same time, a comprehensive study that—in addition to the most accurate determination of personal exposure to air pollutants—would simultaneously examine the widest possible range of biomarkers indicating the effect has not yet been conducted. Such a study is, of course, very expensive, requiring a large investment of time and energy, with close cooperation of many specialists and a large involvement of the persons participating in the study.

In this article, the authors went through the most important aspects of such a study, starting from the personal sampling, through the criteria of selecting the study participants, to the choice and analysis of the markers of exposure and the biomarkers of the effects. We have proposed several techniques for the practical implementation of these measurements. At the same time, the proposed study is far from complete and can be expanded and improved on many points. It is the undisclosed goal of the authors that, later on, this article and the proposed study provide a basis for the implementation of comprehensive research in this field.

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